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Disease-a-Month

Complications of Diabetes Mellitus

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Complications of Diabetes Mellitus

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J. BROOKINS TAYLOR

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DIABETES MELLITUS is a disease that is easy to describe but difficult to define. It is becoming more and more obvious that the laboratory findings so essential to the usual definition are manifestations of a varying pattern of biochemical abnormalities, some of which are poorly, if at all, understood. Persistence of this metabolic disequilibrium leads to progressive clinical and clinicopathologic alterations which may or may not be present in patients with clinical diabetes. These changes are grouped together under the label "diabetic complications"; but on closer inspection this group of disease processes should be subdivided

into three smaller groups, because the problems involved differ widely.

The first group might well be called the *diabetic extremes,* since it includes the result of exaggerated diabetes (i.e., ketoacidosis), as well as the results of vigorous treatment (i.e., hypoglycemia and insulin resistance). The second group could be called *diabetic complexities.* It includes those medical problems, such as infection, surgery and pregnancy, which are common to all patients but are more of a problem in the diabetic patient, where each of the two processes (one diabetic and the other medical) intensifies the other. The third group consists of the true *diabetic complications,* which *(a)* are more or less specific for the disease, *(b)* arise by mechanisms largely unknown, *(c)* pursue a course usually independent of the diabetes itself and *(d)* respond poorly, if at all, to present therapeutic efforts.

KETOACIDOSIS

The incidence of ketoacidosis varies from place to place, and the mortality rate has been reported as high as 31% (2). Among patients observed by us (23), it has been 7.62% (14.25% of those comatose on admission, 4.65% of those semicomatose). The development of ketoacidosis implies nearly complete absence of endogenous insulin and hence occurs more commonly in the juvenile type of diabetes than in the maturity-onset type. Common precipitating factors are: *(a)* omission or inadequate doses of insulin; *(b)* infections, particularly those associated with leukocytosis and/or fever; *(c)* vomiting and diarrhea, or any other cause of fluid and electrolyte depletion; *(d)* anesthesia and shock; *(e)* thyrotoxicosis; *(f)* pregnancy and its toxemias; and *(g),* in some unstable diabetics, insulin hypoglycemia, which may lead to a temporary state of insulin resistance which may go on to actual ketoacidosis.

The basic biochemical defect is a severe impairment of carbohydrate utilization and a marked outpouring of glucose from the liver. The mechanisms by which these changes lead to the familiar clinical and laboratory findings of diabetic ketoacidosis are shown schematically in Figure 1.

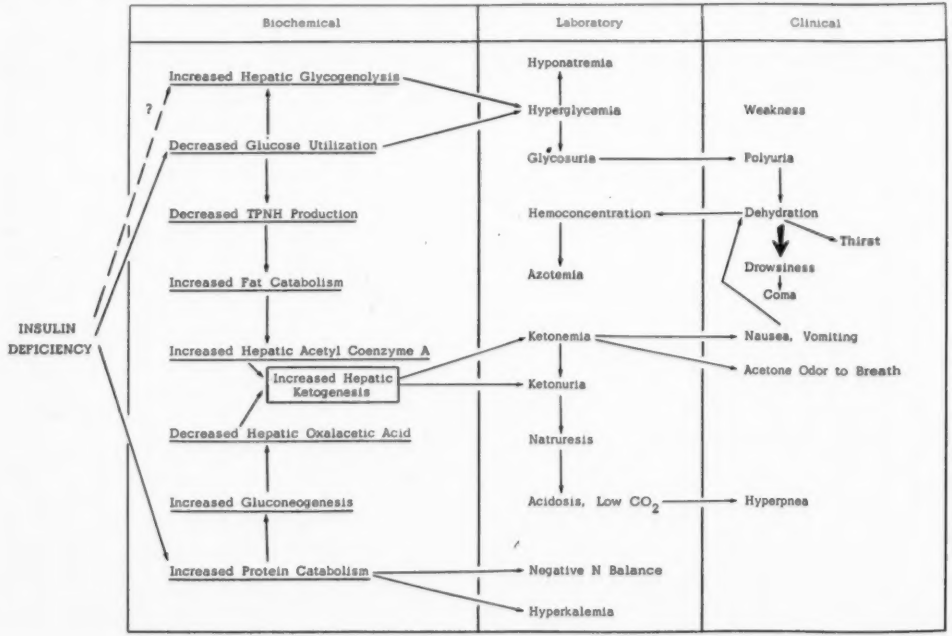
Biochemical
Laboratory
Clinical
INSULIN DEFICIENCY
?
Increased Hepatic Glycogenolysis
Decreased Glucose Utilization
Decreased TPNH Production
Increased Fat Catabolism
Increased Hepatic Acetyl Coenzyme A
Increased Hepatic Ketogenesis
Decreased Hepatic Oxalacetic Acid
Increased Gluconeogenesis
Increased Protein Catabolism
Hyponatremia
Hyperglycemia
Glycosuria
Hemoconcentration
Azotemia
Ketonemia
Ketonuria
Natruresis
Acidosis, Low CO_2
Negative N Balance
Hyperkalemia
Weakness
Polyuria
Dehydration
Thirst
Drowsiness
Coma
Nausea, Vomiting
Acetone Odor to Breath
Hyperpnea

FIG. 1.

The primary result of the insulin lack is impaired glucose utilization in the periphery, together with increased hepatic glycogenolysis (exactly how the latter is mediated is still not clear). The deficient glucose oxidation means deficient reduction of the cofactor triphosphopyridine nucleotide (TPN to TPNH); and since this cofactor is necessary for fatty acid synthesis, the net result is increased fat breakdown to acetyl coenzyme A. Since the increase in glycogenolysis seems to evoke an attempt to compensatory gluconeogenesis, there is not enough oxalacetic acid available to carry this surfeit of acetylcoenzyme off via its usual channel, i.e., the Krebs cycle. The acetyl coenzyme A molecules condense to form ketone bodies which are released from the liver in large quantities. Their utilization in the periphery and excretion in the urine, while active, never quite keep pace with the rate of hepatic production.

The laboratory findings are not unexpected in view of these underlying biochemical changes. However, the pathologic physiology leading to such symptoms as drowsiness, nausea and weakness is obscure. The arrows shown in Figure 1 should be regarded as reasonable opinion rather than unchallengeable fact.

The clinical manifestations of acidosis and coma are variable, but the usual course begins with malaise, abdominal pains, nausea, vomiting, polyuria and sometimes headache. If the polyuria ends in anuria, the prognosis becomes grave. Dehydration may produce a dry mouth and tongue, poor skin turgor and soft eyeballs. The hyperpnea of acidosis (Kussmaul respiration) represents the body's attempt at respiratory compensation.

The easiest laboratory test for confirmation of the diagnosis is the finding of intense glycosuria and ketonuria. However, blood chemistry determinations are much more valuable as a guide to treatment, specifically the ketone, sugar and carbon dioxide content. The blood sugar, which may vary from 200 to 1,200 mg./100 cc. is a poor index of the severity of the ketoacidosis. The carbon dioxide content correlates much better; when it falls below 10 mM./L., the prognosis becomes increasingly grave. Other characteristic findings include a lowered blood pH (6.90–7.30), an initial hyperkalemia (4.5–7.5 mEq./L.), a mild azotemia and often hyponatremia. The latter is due partly to natruresis and partly to dilution of extracellular sodium by

fluid drawn from the intracellular space by the osmotic effect of the hyperglycemia. Since intracellular fluid is essentially sodium-free, the concentration of sodium in the blood will fall out of proportion to the change in total body sodium. Overzealous attempts to correct for all the calculated sodium loss are useless and will result in hypernatremia, once the hyperglycemia is overcome. Leukocytosis is often present, and the urine may contain albumin and hyaline casts.

The differential diagnosis is important. Insulin shock is usually associated with good hydration, profuse diaphoresis and oliguria with negative urine sugar and acetone. If the differential diagnosis cannot be made easily, venipuncture for obtaining blood sugar and injecting glucose will often resolve the doubt; in the case of hypoglycemia, there is prompt improvement, while in the case of acidosis, no harm is done and a chemical diagnosis is soon made. Uremia and cerebrovascular accidents can usually be distinguished by history and physical examination; but if these are not conclusive, emergency laboratory analyses should be done. Uremia results in acidosis but not in hyperglycemia or ketosis. Although a cerebrovascular accident may sometimes cause hyperglycemia, acidosis and ketosis are usually absent or minimal. Rarely will diabetic patients with marked renal insufficiency develop ketonemia and acidosis without much ketonuria.

The treatment of diabetic ketoacidosis is one of the truly critical medical emergencies and is probably the most demanding of all. The essential features of treatment are: the constant attendance of the physician; the completion of the history taking and the physical examination after treatment is begun; the maintenance of a careful record of the patient's clinical and laboratory progress; and the recognition of the need to adjust the treatment, hour by hour, to the changing demands of the patient's condition.

INSULIN.—The four cornerstones of treatment in diabetic ketoacidosis are: insulin, fluid and electrolytes, nutrition and adjuvant measures. Depending on the patient's condition, the initial dose of regular insulin may be 100–400 units, administered intravenously. Thereafter, a dose of 100–200 units is given every 30–60 minutes. The clinician's over-all assessment of the severity of the coma should dictate both the size and the frequency of the

insulin dose. Lee and Duncan (17) have used the bedside-checked plasma acetone (tested with a crushed Acetest tablet or nitroprusside) as a guide for insulin therapy. Blood is drawn for this purpose every hour, and the patient is given 100 units of regular insulin for each serial plasma dilution which still gives a strongly positive reaction. After the dehydration has been partially corrected, a part or all of the dose may be given subcutaneously. In the initial phases of treatment, the administration of too much insulin is rarely a problem, because satisfactory lowering of blood and urine sugar and ketones requires several hours at least. One is less likely to make mistakes by starting with a generous dose and repeating it regularly than by starting in a desultory way and then blindly increasing the dose progressively as the hours pass without any signs of improvement (22).

FLUIDS AND ELECTROLYTES.—Fluid and electrolyte therapy should be planned so as to restore body losses incurred during the development of full-blown ketoacidosis. Martin and her coworkers (18) have determined these losses to lie in the following range: water, 70–120 ml./kg.; sodium, 7–10 mEq./kg.; potassium, 2–3 mEq./kg.; chloride, 5 mEq./kg.; HCO_3^-, 4–5 mEq./kg.; phosphorus, 1 mM./kg.; and magnesium, 0.2 mg./kg. Similar values have been obtained by others (14), as shown in the accompanying table.

LOSSES OF WATER AND ELECTROLYTE DURING DIABETIC COMA IN A 70 KG. (154 LB.) MAN*

	Extracellular Water		Intracellular Water		Total	
	Gm.	% of Total	Gm.	% of Total	Gm.	% of Total
H_2O	3,810	27	3,830	11	6,866	14
	mEq.		mEq.		mEq.	
Na	591	28	26	7	351	15
K	7.8	14	490	9	493	9
Ca	...	...	...	...	252	0.002
Mg	...	...	58	6	56	2
Cl^-	420	25	...	...	430	26
$PO_4^=$	...	...	...	...	344	0.006

*Average values compiled from Joslin, E. P., *et al.*: *Treatment of Diabetes Mellitus* (10th ed.; Philadelphia: Lea & Febiger, 1959).

Actually, it is not absolutely necessary to be precise about these replacements; innumerable patients, without doubt, have done very well with no more treatment than generous quantities of isotonic saline solution. If a selection of parenteral fluids is available, however, it is preferable to give isotonic saline solution

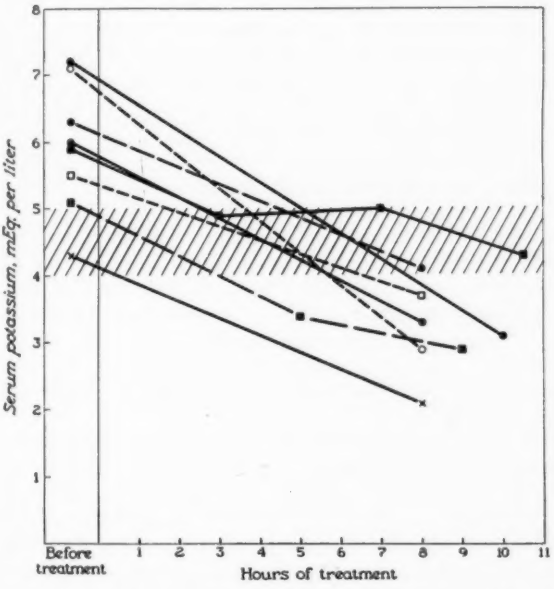

FIG. 2.—Changes in concentration of potassium in extracellular fluid, as measured in blood serum, during treatment of diabetic acidosis in 8 patients. The shaded area indicates the normal range. (From Sprague, R. G., and Power, M. H.: Electrolyte metabolism in diabetic acidosis, J.A.M.A. 151:970, 1953.)

and Ringer's lactate as the first 4 L. of fluid, using less saline and more Ringer's solution. If the acidosis is severe, 1/6 M sodium lactate or 5% sodium bicarbonate is preferable. Thereafter 5% fructose or invert sugar in a balanced hypotonic electrolyte solution is recommended. Lactate combats the acidosis because the

anion is metabolized, leaving an unbalanced cation (sodium) to neutralize the ketone bodies. Untreated hyperglycemia produces a urinary loss of water in excess of electrolytes; treatment of hyperglycemia causes a shift of glucose (and water in excess of electrolytes) into the cell. The sum of these changes is intense extracellular hyperosmolarity, and this is why hypotonic solutions are preferable to isotonic.

Potassium.—The initial hyperkalemia becomes hypokalemia as the ketosis comes under control, owing to *(a)* movement of potassium into cells and *(b)* increased output of potassium in the urine. This trend, illustrated in Figure 2 (28), may be associated with severe symptoms. If serum electrolytes are not readily available, serial electrocardiograms may herald the advent of hypokalemia by characteristic diminution and loss of P waves. It is wiser to prevent this problem (by beginning potassium therapy about the 3d or 4th hour of treatment) than to treat it after it becomes manifest. If the urinary output is adequate, the patient should receive 150–250 mEq. of potassium in the first 24 hours. Intravenous potassium should never be given faster than 30 mEq./hour or in solution more concentrated than 60 mEq./L.

The most physiologic replacement fluid, of course, is blood, but, as a rule, clinicians reserve transfusions for those patients who present in shock.

Glucose.—Nutrition becomes a therapeutic problem at three different stages of treatment. The first problem is *when to give carbohydrate,* and the consensus nowadays is to wait until the glycosuria and polyuria begin to show signs of improvement. Since there is sometimes a rather brisk response to insulin at this time, the patient is protected from any hypoglycemia if intravenous glucose is being administered. Lactate solution is, of course, a source of carbohydrate, but its use should not be delayed if indicated because of acidosis (5). The second problem is *what to give to the patient* just beginning to take oral nourishment. For the first 4–6 hours it is advisable to give only small frequent feedings of clear liquids and crackers. Gastric dilatation, if present, should be treated before feeding the patient. If this hurdle is successfully passed, the third problem, *beginning a planned diabetic diet,* becomes very simple and can be done at the next convenient mealtime.

Adjuvant therapy in diabetic acidosis is determined by the presence of associated disease. This is why it is important to complete the history and physical examination after treatment is begun, when the physician is less likely to overlook associated conditions because of his anxiety to begin treatment. This is the time to look for hidden infections, vascular accidents and renal insufficiency, for example, and to institute appropriate treatment. It is also a good time to ascertain whether gastric atony and dilatation are present and whether it will be necessary to pass a nasogastric tube for decompression.

If the patient makes a good recovery from ketoacidosis during the first 12 hours, he may still run some risk of recurrent ketosis or hypoglycemia. The best way to prevent this risk is by *(a)* periodically testing the urine for sugar and acetone, *(b)* injecting regular or crystalline insulin accordingly and *(c)* giving the patient some carbohydrate. This should be done every 4–6 hours throughout this period. Long-acting insulins should not be given until the patient is completely out of ketoacidosis and eating satisfactorily.

HYPOGLYCEMIA

Hypoglycemia occurs in diabetes only as a complication of treatment; usually it is due to treatment with insulin, but occasionally the oral antidiabetic agents, particularly chlorpropamide, may be responsible. Common causes of hypoglycemia are: *(a)* too much insulin, *(b)* skipped or skimped meals or *(c)* excessive exercise. Sometimes the patient with "brittle" diabetes develops hypoglycemia presumably because of sudden release of insulin previously bound to antibodies. Hypoglycemia in diabetics occurs primarily as a result of increased peripheral glucose utilization in the case of insulin, and perhaps as a result of decreased hepatic glucose output in the case of the sulfonylurea drugs; however, there is some evidence that both mechanisms may be active in each case. The immediate cause of symptoms is metabolic starvation of the central nervous system, with secondary increase in vagal tone, epinephrine secretion and adrenocortical secretion.

Hypoglycemia produces, in succession, personality changes (depression, negativism and irritability), hunger, sweating, tachycardia, tremors, twitching and even convulsions or unconscious-

ness. The garrulous, quarrelsome, combative behavior of some patients has sometimes led to arrest on the grounds of intoxication. With long-acting insulins, the hypoglycemia often occurs during the hours of sleep. These drugs may be the cause of nightmares, night sweats, sleep walking, early-morning headache or psychotic behavior. Occasionally there are localized neurologic findings which suggest a vascular accident. They can be distinguished by their rapid regression with treatment.

An unconscious patient with no accompanying history should always be examined carefully for needle marks, which may provide the clue to the diagnosis of insulin hypoglycemia. Immediate treatment consists of the giving of sugar, candy or sweetened juice if the patient can cooperate and of intravenous glucose if he cannot. The recurrence of symptoms may require the administration of additional carbohydrate. The patient should eat a normal meal, or milk and crackers, as soon as possible thereafter, especially if he is taking a long-acting insulin. Subcutaneous epinephrine may be temporarily effective if glucose is not at once available. Recent experiences in psychiatric centers have shown that the response to intravenous glucagon may occur sooner, and is more satisfactory, than the usual treatment with exogenous carbohydrate.

When the hypoglycemia is due to chlorpropamide, the persistently high drug levels may give rise to recurrences for a surprisingly long time. One of us has seen such a patient, admitted unconscious during the day, who developed severe hypoglycemia each night for the next three nights even in the absence of any additional hypoglycemic agents. Phenethyldiguanide has an anorexigenic effect which may predispose to hypoglycemia when administered along with the accustomed dose of insulin.

Unless unusual exercise or skipped meals can be incriminated, the occurrence of hypoglycemia demands a change in the patient's management, for two reasons: (1) Repeated hypoglycemia (if severe) frequently leads to progressive cerebral deterioration, which is completely irreversible. When this is the result of well-intentioned attempts at "perfect" control, it is particularly tragic. (2) The starvation of the central nervous system triggers a number of mechanisms, such as increased anterior pituitary and adrenocortical discharge, increased epinephrine release and perhaps glucagon release. A temporary insulin an-

tagonism results, with an apparent exacerbation of the diabetes. If the physician counters by increasing the dose of insulin, he may set in motion a vicious metabolic cycle—and this means that, at best, the patient is taking more insulin than he really needs; at worst, his life is being made miserable with repeated reactions or even precipitate acidosis (27).

The best treatment for hypoglycemia is prevention, which means education of the patient and the use of divided doses of insulin with night feedings, if he takes more than 50–60 units daily. Mild hypoglycemia can often be eliminated by increasing and/or redistributing the carbohydrate content of the diet. Patients taking sizable doses of insulin would do well to carry hard candy and the familiar "I am a Diabetic" card.

INSULIN ALLERGY AND RESISTANCE

Insulin, like any other foreign protein, can produce antibodies and allergic manifestations. This field is being explored with increasing interest, and the many confusing findings have been well summarized by Berson and Yalow (1). Briefly, there appear to be *(a)* insulin inhibitors, present in serum globulins and presumably normally present in response to hypoglycemia; *(b)* insulin antagonists, found in the alpha globulin fraction from patients in diabetic acidosis; *(c)* insulin-binding antibodies found in the beta-to-gamma globulin zone or the gamma globulin fraction of the sera of all insulin-treated patients, particularly those with insulin resistance; and *(d)* skin-sensitizing antibodies, occurring in the beta globulin fraction.

Insulin allergy, localized or generalized, may be treated by antihistamine administration, by changing the animal source of insulin or by standard desensitization technics. Insulin resistance is a more serious problem, sometimes requiring enormous doses of insulin for control of the diabetes (12).

Intensive treatment with adrenal corticosteroids and/or oral hypoglycemic agents has been helpful occasionally in reducing the insulin requirements of the patients showing insulin resistance (4). The action of the adrenocortical hormone in this situation is to prevent or minimize antibody formation, and its potential usefulness must be weighed against its known diabetogenic effect.

INFECTION IN THE DIABETIC PATIENT

The diabetic patient, particularly if his disease is poorly controlled, is more susceptible to infection than the normal individual. Urinary tract infections, furuncles and carbuncles, intertrigo and vaginitis, mucormycosis and tuberculosis are some prime examples. Vigorous attempts to control the diabetes are essential to successful treatment of the infection in these cases.

Deterioration of previously good diabetic control is a sequel of most infections, especially those associated with leukocytosis and/or fever. If anorexia or a gastrointestinal upset is also present, the stage is set for the development of ketosis. The mainstay of treatment in such a situation is generous amounts of regular insulin. The oral hypoglycemic agents or even the long-acting insulins are usually ineffective in the presence of infection. It is imperative that every diabetic be informed of these facts.

The diabetic with an infection requires careful attention to nutrition and hydration. The use of an antibiotic should be determined by the sensitivity of the infecting organism, and free drainage of localized infections is imperative.

The coexistence of diabetes and tuberculosis is more than a casual coincidence (8). The incidence of tuberculosis in juvenile diabetics is 10 times higher than in the control population. All juvenile diabetics should have an annual x-ray examination of the chest. Susceptibility appears to be greater in diabetics who are poorly controlled, and these patients have a poor prognosis unless the diabetes can be well controlled.

Because of the chronic fever and toxicity, the tuberculous diabetic patient should receive a generous supply of calories. Insulin treatment should be adjusted until the patient is euglycemic throughout as much of the day as possible. If these conditions can be met, the prognosis of the tuberculous infection is equal to that in the nondiabetic patient.

Urinary tract infections are a hazard to the diabetic patient because they are so frequently overlooked despite their very serious implications. Pyelonephritis probably occurs sooner or later in 20–40% of the diabetic population, often initiated by the frequently unnecessary introduction of a catheter. Once pyelonephritis is diagnosed, the patient deserves every possible effort to identify and eradicate the infecting organism. Aside from the

well-known uremic sequelae to chronic pyelonephritis in any patient, the diabetic patient runs an added risk of an even graver renal complication—renal papillary necrosis (26). This complication should be considered in any patient, with or without diabetes and pyelonephritis, who presents with renal colic, gross hematuria and oliguria. The passage of papillary tissue in the urine or the characteristic sling sign* on retrograde pyelography is confirmatory. The condition is often fatal and demands immediate attention by a urologist. Nephrectomy has sometimes proved lifesaving.

SURGERY

The diabetic patient undergoes surgery with three handicaps: (1) the vascular or renal complications of diabetes, if present, increase the anesthetic and operative risks; (2) the disease requiring surgery may have already upset diabetic control to some extent; and (3) treatment of diabetes during the postoperative period requires close, individualized attention. A fourth problem is that the division of responsibility for control of the diabetes among the physician, the surgeon and the anesthetist is likely to lead to confusion and omissions, unless special efforts are made to avoid these situations.

In preoperative management, the physician must assess the integrity of the cardiovascular system, see that the diabetes is as well controlled as possible, and see that surgery is delayed, if possible, until the patient is in optimum condition. The patient who is well controlled up to the time of operation needs no extra preparation.

The physician must consult with the anesthetist about the choice of anesthesia, preferring local to spinal, spinal to general and cyclopropane to ether.

Patients taking oral hypoglycemic agents or long-acting insulins should receive their last dose on the day before operation. During surgery the patient should receive 20–30 units of regular insulin

*Demarcation and separation of a papilla may result in the appearance of a ring or arcade of radiopaque material ("sling sign") curving through the area of the papilla, as visualized by retrograde pyelography. Various other x-ray abnormalities of the papillary contour have been described, but they are not specific.

in each liter of 5% glucose. Surgery should be as brief, atraumatic and nonshocking as is consistent with the operative findings. Careful nursing attention and periodic evaluation of the patient's condition are essential during the recovery from anesthesia and the postoperative period.

During this period the patient should be treated as if he were recovering from ketoacidosis. This means that the urine (and the blood, if necessary) should be examined every 4–6 hours for sugar and acetone. Mild glycosuria during these few days is not undesirable, because it minimizes the risk of hypoglycemia. The physician should plan for the administration of oral or intravenous fluids containing a carbohydrate around the clock. If this is done, the patient can be safely given regular insulin every 4–6 hours, according to the degree of glycosuria. It is imperative that any excessive fluid or electrolyte loss due to drainage tubes or nasogastric suction be carefully and completely corrected on a day-to-day basis.

Once the patient has demonstrated his ability to take regular oral feedings, he can be put on liquids, then on bland feedings and finally back on his own diabetic diet. Then, unless he is febrile, long-acting insulin or the oral hypoglycemic agents can be restarted.

PREGNANCY

The young female diabetic patient faces three threats to successful motherhood: spontaneous abortion, stillbirths and neonatal deaths. Sterility is rarely seen today. Fortunately, the physician of today is better able to protect the patient from these threats.

Initially, the decision to have children may not be easy. If both parents are diabetic, the child will very likely develop diabetes early in life, and the parents must make their own decision in their knowledge of that eventuality. The incidence of diabetes in the offspring is roughly one in four if only one parent is diabetic. If infertility is a problem, the physician should give particular attention to the diet and the diabetic control. Gonadotropins, like other pituitary hormones, are complex proteins; their synthesis in the anterior pituitary may be surprisingly sensitive to moderate

impairment of protein anabolism, such as may occur in uncontrolled diabetes.

There is an increased incidence of spontaneous abortion in the poorly controlled diabetic, and especially in those with ketoacidosis. Good control is sometimes difficult to maintain. The changing insulin requirements during pregnancy may be summarized as follows: *(a)* decreased in the first trimester, *(b)* normal in the second trimester, *(c)* increased in the third trimester and *(d)* a prompt fall in insulin requirement to normal levels after delivery.

The pregnant diabetic patient usually has a lowered renal threshold for glucose during pregnancy, and ketonuria seems to occur readily. Because of these variables, the physician should see the pregnant diabetic patient every 2–4 weeks throughout pregnancy and adjust her diabetic therapy accordingly. There has not been much experience with the oral hypoglycemic agents, probably because most diabetic patients young enough to bear children do not respond to these agents. A recent report raises the possibility of transplacental circulation of the sulfonylureas and resulting fetal mortality (16). In our present state of knowledge, use of these agents during pregnancy is probably inadvisable.

White and her co-workers (30) have laid great emphasis on possible endocrine imbalance in the pregnant diabetic patient. They have found that abnormal elevation of maternal chorionic gonadotropin levels and depression of pregnanediol excretion correlated inversely with the prognosis as regards fetal mortality. They have presented a wealth of data showing that careful treatment with estrogen and progesterone markedly improves fetal salvage. Eventually this treatment was simplified by the elimination of repeated hormone assays and use of increasing doses of stilbestrol alone. It is interesting that in a more recent study, performed under the auspices of the Medical Research Council of Great Britain, (24) 147 pregnant diabetic patients were divided into two groups at random, one group being treated with graduated doses of ethisterone and progesterone and the other given no treatment. The incidence of stillbirth, neonatal death, fetal malformations, hydramnios, edema and albuminuria was approximately the same in each group. In summary,

hormone therapy is probably unnecessary in the pregnancy of an uncomplicated diabetic patient. In more complicated situations, its use should not be neglected even though the question of its effectiveness is still unsettled.

We believe that it is highly important to follow these patients closely in order to correct the dosage of insulin or any other situation that may arise promptly and that they should be seen often by the physician and obstetrician. This, in our opinion, is fundamental regardless of hormone therapy (21).

To minimize the risk of stillbirths, most authorities recommend early delivery, at about the 37th or 38th week in the case of the average diabetic patient and as early as the 35th week if extensive pelvic vascular disease is present. Emergency delivery may be necessitated by *(a)* pre-eclampsia, *(b)* hydramnios, *(c)* fetal halo* and *(d)* absence of fetal motion and good fetal heart sounds. Usually the decision as to pelvic versus cesarian delivery lies with the obstetrician and is influenced by such factors as toxemia, cephalopelvic disproportion and abnormal presentation. Anesthesia in any case is preferably spinal. The management of diabetes at this time is the same as for elective surgery.

During the neonatal period, the infant born under these conditions should be considered a large premature baby (19, 31). Much of the overweight of these infants is due to water retention. Another complication is hyaline membrane disease; and to successfully handle this complication, the attending pediatrician must have a high index of suspicion and an aggressive approach. Several authors have mentioned an increased incidence of fetal abnormalities. Hypoglycemia, formerly considered to be serious threat to the infant, is now thought to occur rarely. These problems are all transient. The prognosis for an infant surviving the first 36 hours is the same as that for the normal infant. As a matter of fact, a large baby is a good clue to the presence of diabetes in either parent, and quite frequently this is true of the prediabetic state as well. Any woman who has large babies consistently should be considered in the prediabetic state. Glucose

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*A halo around the head of the fetus, on x-ray examination, which is supposed to indicate an excess amount of fat and is one of the recommended reasons for early delivery.

tolerance tests frequently indicate abnormality before these patients develop clinical diabetes.

COMPLICATIONS PECULIAR TO DIABETIC PATIENTS

Approximately 3 out of every 4 diabetic patients die of vascular disease, which includes the following pathologic processes: *(a)* lesions of the medium-sized arteries, especially of the myocardium, lower limbs and brain; *(b)* lesions of the arterioles; and *(c)* lesions of the capillaries, especially of the glomeruli and retina, and perhaps of the nerves.

The process in the arteries has usually been considered to be morphologically identical to nondiabetic atherosclerosis. However, a recent study (10) suggests that the process may be different in the diabetic patient, in whom it is characterized by endothelial proliferation and deposition of a mucopolysaccharide material distinctly different, both in distribution and in staining characteristics, from the mucopolysaccharide seen in arteriosclerosis without diabetes. This lesion is apparently characteristic of the arteriolar changes in diabetic nephropathy and in neuropathy also.

Progression of these lesions causes *(a)* narrowing of the vascular lumen, *(b)* development of collateral circulation, *(c)* thromboses, *(d)* ischemia and anoxia and *(e)* tissue necrosis or gangrene precipitated by thermal injury, trauma or infection. Until the end stages of the disease, there may be few symptoms, aside from a varying degree of intermittent claudication. Hypesthesia of the feet and legs may be an accessory factor in the precipitation of gangrene; the patient may not be aware that he is bruising or chafing his toes with ill-fitting shoes or burning them in his ill-advised attempts to warm up his cold feet. Examination of the extremities usually reveals evidence of ischemia to the trained observer: *(a)* loss of hair on the toes, *(b)* thickening and curving of the toenails, *(c)* absent or diminished pulsations, *(d)* coldness and dusky cyanosis of the feet and *(e)* muscle atrophy. Careful assessment of these changes will show that their incidence, severity and progression may vary widely in the average diabetic population.

The best treatment for peripheral vascular disease is to combat all factors which would tend to accelerate it, and this requires education of the patient. He must understand the need to wear clean, dry, warm socks and shoes, which are neither so tight as to cause undue pressure nor so loose as to chafe the feet. He must be taught to trim his nails properly to avoid ingrown nails; to treat corns and calluses as circumspectly as possible; to avoid the use of hot soaks or applying hot water bottles to the feet; and to carry out Buerger's exercises. Once gangrene has occurred, conservative treatment with strict rest, tepid soaks and local antibiotics should be tried. In many cases, however, this will not be effective and amputation will be required. Some patients can be fitted with a prosthesis later, while others are best left alone because of their age or the perilous condition of the other leg. If circulatory compromise is relatively localized, vascular grafting may be performed with marked benefit.

The problems of management of the diabetic patient, with his increased tendency to multiple cerebrovascular accidents or myocardial infarctions, are the same as in the nondiabetic population: prevention is uncertain, treatment is entirely supportive, and the prognosis is discouraging.

Renal Complications

Arteriosclerosis in the renal vasculature, particularly in the afferent and efferent vessels of the glomeruli, occurs as a hyaline thickening of the media. These changes are seen in both diabetes and hypertension, but they are most frequent where the two conditions coexist.

The capillary lesions in the kidney of the diabetic patient were originally described by Kimmelstiel and Wilson (15), whose names became attached to both the morphologic lesion and the clinical syndrome. This has led to the incorrect assumption that the one was the cause of the other.

What Kimmelstiel and Wilson described, and called "intercapillary glomerulosclerosis," are rounded hyaline masses, 20–120 microns in diameter, in the centers of the glomerular capillary loops. Subsequent studies of these masses over the course of 24 years have yielded the following facts: *(a)* they occur typically at the periphery of the glomerulus; *(b)* usually they occur only

on the inner, or central, aspect of the capillary loop; *(c)* they probably begin within the endothelial cells of the capillary; *(d)* as the lesions progress, they usually obliterate the capillary lumen, leaving one or more layers of nuclei in the periphery of the nodule; *(e)* they have the staining characteristics of collagen and reticulin; and *(f)* they appear to be specific for diabetes mellitus.

Another lesion of the diabetic glomerulus is so-called "diffuse diabetic glomerulosclerosis," described by Fahr (6). These lesions *(a)* thicken the capillary loop in a symmetrical circumferential manner, *(b)* probably arise as a thickening and convolution of the basement membrane and later spread to involve the endothelial and epithelial cells, *(c)* contain endothelial nuclei buried uniformly throughout the hyaline tissue, *(d)* have the staining characteristics of collagen but not of reticulin and *(e)* may occur sometimes in the absence of diabetes.

A third glomerular lesion, the so-called "fibrinoid crescent," occurs late in the course of renal disease, especially in association with hypertensive vascular disease, and contains lipid and mucopolysaccharide but no evidence of cellular origin. This lesion is believed to be of the same material that is present in arteriolonecrosis, and to have reached its position in the glomerulus by embolization.

Kimmelstiel and Wilson noted that their cases of nodular glomerulosclerosis occurred in a clinical setting of diabetic nephropathy, manifested by albuminuria, edema, impaired renal function tests, uremia, and hypertension; and the course of the glomerulosclerosis was that of gradually progressive renal failure with a fatal outcome. It is imprecise to call this the "Kimmelstiel-Wilson syndrome." Many of these patients do not have any of the nodular masses originally described, while other patients with numerous nodular lesions are asymptomatic. Furthermore, the degree of involvement by the lesions of diffuse glomerulosclerosis does correlate well with the severity of the clinical picture, even in those rare instances where it is not due to diabetes. It seems advisable to retain the term "Kimmelstiel-Wilson lesion," which is indeed specific for diabetes, but to abandon "Kimmelstiel-Wilson syndrome" in favor of "diabetic nephropathy," which appears to be caused by diffuse glomerulosclerosis (9, 20).

The treatment of diabetic nephropathy is discouraging and, as in the case of peripheral vascular disease, consists mainly of

not accelerating the course of the disease. A low-protein diet is essential, and in some cases the rice diet has been remarkably effective. Transfusions should be used only in case of severe anemia. Any urinary tract infection should be treated with the utmost vigor.

Does diabetic nephropathy affect the course of the diabetes? Some authorities feel that such patients are easier to control on the same or smaller doses of insulin; others maintain that these patients are really ingesting fewer calories because of anorexia and dietary changes and that their consequent weight loss is masked by the accumulation of edema. Because the renal threshold for glucose is elevated, urinalyses are poor guidelines for clinical control.

Ocular Complications

Because of the psychologic implications of blindness, the threat of diabetic retinopathy may loom as large to the diabetic patient as that of the life-threatening but insidious nephropathy. Unfortunately, these conditions generally tend to accompany each other, in varying degrees of severity (7). Exhaustive pathologic studies of both renal and retinal tissue at necropsy have shown retinopathy in 100% of the patients with the Kimmelstiel-Wilson lesion, but the lesion itself appeared in only 58% of the patients with retinal microaneurysms.

These saccular dilatations, 30–90 μ in diameter, arise from the venous side of the capillary bed in the inner nuclear layer. Later the veins may also be involved, by dilatation, tortuosity and beading; the arteries occasionally show sclerosis. As time passes, creamy or "waxy" exudates appear, often in a pattern paralleling the vessels. Hemorrhages occur later, varying widely in size, shape and distribution. When these hemorrhages extend into the vitreous body, they stimulate a proliferation of capillaries and fibroblasts; the eventual contraction of this fibrous tissue is often the cause of retinal detachment. This extensive neovascularization (retinitis proliferans) is often severe enough to cause blindness even when it is confined to the retina. Secondary glaucoma may complete the picture. If the patient has severe hypertensive vascular disease and/or diabetic nephropathy, the vascular changes

of hypertension and uremia may also be found on fundoscopic examination (29).

Therapy for diabetic retinopathy is a difficult problem. Some ophthalmologists believe that all the changes may progress and regress spontaneously, except that retinitis proliferans itself is almost always irreversible. Obviously, the best treatment will be that which prevents the appearance of neovascularization and induces regression of the other lesions. Such an ideal treatment is not yet available. Many forms of drug therapy—e.g., ascorbic acid, vitamin B_{12}, cortisone and testosterone—have been used without success. Adrenalectomy and hypophysectomy have been used with slight and moderate success. Perhaps better results could be obtained if the patients were operated on earlier; but, paradoxically, few physicians could advise surgery for the milder cases without more encouraging data. More recent attempts at rigid control of dietary fat appear promising, and this may be the direction of future progress.

The other ocular complications are less serious. In the uncontrolled diabetic patient with wide swings in blood sugar, the glucose content of the lens varies widely and frequently. This affects the refractive power of the lens, owing to the change in the osmotic effect, and causes a varying refractive error. It is useless to attempt to correct for this error until the diabetes is well controlled.

Another effect of the high glucose content of the lens is the increased incidence of senile cataracts. These tend to mature rapidly and to increase in frequency and severity with the duration of the diabetes.

Neurologic Complications

A third major complication of diabetes is a poorly understood disturbance of nerve function (5). It is customary to explain these changes as secondary to vasculitis of vasa nervorum, and there is considerable morphologic evidence to support this view. However, the role of lipid and phospholipid metabolism in neurologic structure and function is vital but poorly understood; a disturbance here, as might well occur in diabetes, could possibly have far-reaching effects. Certainly, the partial reversibility of most

cases of diabetic peripheral neuropathy argues against a purely vascular etiology.

The most common form of neuropathy is acute or chronic neuritis, usually involving the feet and legs in a fairly symmetrical way. The symptoms progress from hypesthesia to paresthesia to a chronic aching, superficial or deep, usually worse at night. There may also be loss of superficial and deep tendon reflexes, motor weakness and even muscular atrophy.

Another serious problem is autonomic neuropathy, which may cause postural hypotension, poor intestinal motility, nocturnal diarrhea, decreased sweating, bladder and sphincter dysfunction and impotence. Rarely, trophic effects may be prominent, taking the form of osteoporosis of the extremities or even of a diabetic Charcot's joint.

A third site of neurologic damage is the central nervous system itself. Bizarre mental disturbances may be prominent. Loss of position and vibration sense are often present, indicating posterior column disease. Cranial nerve palsies are not uncommon; and, rarely, the sudden onset of diabetic myelopathy may simulate spinal cord transection. In all these situations and in many cases of peripheral neuropathy, there is elevation of the spinal fluid protein, often to more than 100 mg./100 cc.

Treatment of all these neuropathies is rarely successful. Every drug that has ever been efficacious in any other type of neuropathy has at one time or another been advocated for diabetic neuropathy; the list includes thiamine, pyridoxine, vitamin B complex, vitamin B_{12}, crude liver extract, pregnant mammalian liver extract and BAL. If the physician is enthusiastic in his approach, a fair degree of improvement usually follows treatment with any of these agents. The response is incomplete unless the neuropathy began in association with a sudden loss of diabetic control which was restored to normal in a matter of days, or a few weeks at the most.

Dermatologic Complications

Skin disorders associated with diabetes may be either infectious or metabolic in origin. In a sense, of course, they are all metabolic, since the increased incidence of infections is probably dependent in part on the hyperglycemia. That the skin reflects the blood

sugar can be tested by having an uncontrolled diabetic patient hold a strip of glucose oxidase test paper between his thumb and forefinger; a faintly positive reaction will often occur even though all sweat and skin debris have just been washed off.

Staphylococcal infections (folliculitis, furunculosis, paronychia and carbuncles) are common in diabetes. The resistant staphylococcus is a problem and frequently recurs when antibiotics alone are used. Frequent hot soaks and open drainage are also helpful, and good control of the diabetes is necessary.

Pruritus ani et vulvae, intertrigo and vaginitis are frequent symptoms of uncontrolled diabetes and are usually the result of monilial infection. Epidermophytosis may be a stubborn problem.

The commonest metabolic skin disease in diabetes really involves the subcutaneous fat—the so-called "insulin lipodystrophy," which results from the local effects of injected insulin. The usual lesion is an area of localized fat atrophy, which may be distressing from a cosmetic viewpoint, especially in young women. The mechanism of this atrophy is unknown; the various components of insulin solutions have been studied and exonerated. The best prevention is a careful daily rotation of the injection sites. Many authorities advocate making the insulin injection intramuscular rather than subcutaneous. This is particularly advisable in the other form of lipodystrophy, fat hypertrophy, which is apparently the result of direct insulin action on adipose tissue. Besides its cosmetic drawback, fat hypertrophy is undesirable because a considerable amount of the insulin injected into these areas never finds its way into the general circulation.

Other metabolic skin disorders in diabetes include: xanthosis, a yellowish discoloration of the skin due to increased carotinemia; xanthelasma, a collection of slightly raised, fatty tumors occurring around the eyelids; and xanthoma diabeticorum. The last is a rather rare condition consisting of numerous small red nodules on the extensor surfaces of the arms and legs, near the large joints. They appear to be related to uncontrolled diabetes and/or elevation of the total lipid and cholesterol content of the blood; restoration of normal values by treatment with diet and insulin usually results in complete disappearance of the lesions.

Necrobiosis lipoidica diabeticorum is a chronic condition, occurring in a higher ratio (4:1) in females. It consists of small yellowish papules on the feet, legs, thighs and occasionally the

trunk and upper extremities. These papules tend to enlarge, coalesce, ulcerate centrally and eventually heal with scarring. Pathologically, the lesions consist of collagen degeneration, perivascular inflammation and a deposition of phospholipids and free cholesterol. Treatment is unsatisfactory; however, good control of the diabetes enhances the tendency to spontaneous regression.

ETIOLOGY AND PATHOGENESIS

The inadequacy of our therapeutic efforts in diabetic complications is a result of our inadequate understanding of the etiology and pathogenesis of the basic changes. Apparently, this micropathology will have to be approached by new technics and tools, using all the analytic talents of modern biochemistry. The other approach, that of trying to correlate the development of complications with certain clinical features, has not been satisfactory, except perhaps in a negative way.

Ricketts has surveyed this problem in an excellent article (25) in which he assesses each of the clinical factors which have been correlated with the progress of vascular complications. He finds that there is a definite tendency for arterial disease and nephropathy to occur more frequently in women than in men; this is not true of retinopathy, where the incidence is equal. He discusses also the question of heredity—i.e., whether the patient may inherit a tendency to vascular disease closely linked to a tendency to diabetes. Except for fragmentary reports of a negative nature—e.g., complications accompanying the diabetes of pancreatitis, hemachromatosis and total pancreatectomy—there is at present no body of data which will support a definite decision on this point.

One of the liveliest controversies in clinical diabetes concerns the relationship between diabetic control and diabetic complications. It is too early to say whether such a relationship exists, directly or indirectly. Studies by some of the most conscientious and experienced workers have provided data showing that a certain percentage of diabetic patients will develop vascular disease with time, regardless of their degree of diabetic control. Other authorities, equally conscientious and experienced, have

figures to prove that a correlation does exist. One of these is the excellent article by Hardin and his associates (13) showing that "the only identifiable factor bearing a constantly significant relationship to the incidence and severity of retinopathy is the degree of control of the diabetes" (29). But in any series there are well-controlled cases with severe complications and many poorly controlled cases with no complications. The real problem in studies such as these is how to define "control of diabetes." How is this measured? By urine sugar? By blood sugar? By serum nonesterified fatty acids? By serum mucoproteins and mucopolysaccharides? Or by some unappreciated or unknown substance in the blood? Or, to make matters more complicated, perhaps this key parameter is not a blood level but a tissue level, or an enzyme concentration, or a shift in equilibrium or a change in membrane potential. Logically, clues to the nature of good control should come from our knowledge of the pathogenesis and biochemistry of the vascular lesion. But such knowledge is still too rudimentary. All that we can say is that the level of blood glucose alone is probably one of the least important factors in the development of diabetic complications.

Endocrine effects on the severity of diabetes have been known since the early experiments of Houssay and of Long and Lukens. In recent years an apparently beneficial effect of spontaneous hypopituitarism on retinopathy has stimulated the therapeutic approaches of adrenalectomy and hypophysectomy without dramatic success. It seems unlikely that further work along these lines will disclose why these lesions develop.

Studies of mucopolysaccharide and lipid metabolism in diabetic patients have given confusing, and often contradictory, information as to the importance of these factors in vascular complications. Since our knowledge of these topics is still limited, it may be premature to expect definite answers now. Atheromatosis in the nondiabetic patient, for instance, has been the object of intense research activity all over the world for several decades, and we still have no good laboratory method for predicting or evaluating the degree of vascular involvement of a given individual at a given time.

In ruminating on the extent of our ignorance in this field, it seems safe to say that diabetes mellitus is not a disease but a

metabolic disorder, and not such a strange one at that. As Cahill has commented, "metabolically speaking, the diabetic liver is a fasting liver in which biochemical alterations have become grossly exaggerated" (3). The problem in diabetes is not that the disorder exists but that it does not correct itself spontaneously; that it represents, in effect, a new and abnormal equilibrium. Good, or even adequate, therapy with diet or insulin is effective in shifting the equilibrium toward normal, or at least keeping it from becoming more abnormal; and hence the symptoms are alleviated. Diabetic complications, on the other hand, constitute a real disease with a characteristic pathology, a progression of signs and symptoms and a predictable outcome. What we do not have is a good explanation of the cause and pathogenesis. Logically, this should be related to the abnormal metabolic equilibrium. Perhaps the answer will come when we stop thinking of the equilibrium in terms of biochemical compounds and think of it in terms of energy transfer. Glucose is a vital source of energy for all tissues. If the energy available to a cell or to any of its components (e.g., membrane, mitochondria and microsomes) is inadequate, the functions usually carried out by these organelles are not likely to be performed efficiently. If such functions as membrane permeability, synthesis of complex molecules and active transport are seriously impaired, alternate pathways may lead to the formation and/or accumulation of abnormal materials in certain histologic locations, depending on the histologic location of that function. Then the riddle presents itself differently: Why don't all diabetics develop complications?

The manufacture of theoretical explanations for these problems, like the descent to Avernus, is easy. But to clarify and restate each step in the hypothesis, to exclude alternate explanations, to test each possibility, to fulfill Koch's postulates experimentally, to devise a biochemically satisfactory therapy that is clinically successful—hoc opus, hic labor est.

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